Abstract

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Abstract: *DESCRIPTION* (provided by applicant): Damaged neuronal connections in the adult central nervous system (CNS) do not regenerate. This is due at least in part to the physical barrier formed by glial cells that respond by proliferating and forming a scar and to the presence of inhibitory molecules in the CNS environment. Recent work has shown that the EphA4 receptor tyrosine kinase plays a critical role in the inhibition of axon regeneration that occurs after spinal cord injury. Remarkably, axons in EphA4 knockout mice can regenerate past the site of injury and re-establish severed connections resulting in functional recovery. Other evidence suggests that EphA4 plays an inhibitory role in axonal and dendritic growth in other regions of the central nervous system as well. Furthermore, EphA4 has been implicated in the maintenance of platelet aggregation during thrombus formation and in prostate cancer cell growth. Thus, inhibiting EphA4 function is a very promising new approach with high potential for a number of therapeutic applications. However, EphA4 has not yet been exploited as a target for small molecules. The signaling activity of EphA4 is stimulated by binding several membrane-anchored ligands, called ephrins. As we have recently shown, peptides that antagonize ephrin binding block the physiological activity of the receptor. Furthermore, a pilot high throughput screen performed in the Chemical Library Screening Facility of our Institute on 10,000 compounds has demonstrated the feasibility of screening for small molecules that inhibit ligand binding to EphA4. In this application, we propose to perform a full scale high throughput screen for small molecule EphA4 antagonists and to characterize the potency and selectivity of the active compounds identified. We propose to use an assay protocol similar to the one that was previously successful in our pilot screen. In this assay, we will measure the ability of small molecules to inhibit the binding of an ephrin-A5 alkaline phosphatase fusion protein to the EphA4 extracellular domain immobilized through a carboxy-terminal hexahistidine tag. An advantage of reagents that target the extracellular domain of EphA4 is that they can be highly selective, unlike most tyrosine kinase domain inhibitors, and that they can act without having to penetrate inside the cell.

Thesaurus Terms:
High throughput screening, EphA4 Receptor, tyrosine kinase, Nervous System Repair, CNS, platelet aggregation, thrombus formation, prostate cancer, ephrins, ephrin-A5 alkaline phosphatase, carboxy-terminal hexahistidine

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